Management of Patients with HIV in the Intensive Care Unit

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Because there are more than one million Americans with HIV, intensive care units continue to see frequent patients with HIV infection. In the era of highly active antiretroviral therapy, clinicians must be aware of drug toxicities and drug interactions. They must also recognize traditional opportunistic infections, as well as newer syndromes such as immune reconstitution syndrome, multicentric Castleman's disease, and primary pleural cell lymphoma.

Keywords: HIV; intensive care unit; pulmonary

In the United States, approximately one million individuals are infected with HIV. There are about 40,000 to 60,000 new cases of HIV infection each year (www.cdc.gov/hiv/stats). The epidemiologic profile of patients with HIV infections is shifting in this country. There are a substantial number of homosexual males who are infected in large urban areas, but there is a growing proportion of infected patients who are female, who reside in smaller cities or rural areas, and who have acquired their infection heterosexually or via intravenous drug abuse. There have been changes in the range and frequency of clinical manifestations of AIDS, reflecting issues that affect women, African Americans, and intravenous drug abusers. The population of HIV-infected patients is also getting older: patients with HIV infection benefit from improved management, and live longer. Individuals without HIV infection are also living longer, and are sexually active longer, extending the period of risk for acquiring HIV infection. Thus, a substantial number of residents of the United States have HIV infection, and the spectrum of affected patients is changing.

Individuals with HIV infection are hospitalized, and may ultimately be cared for in intensive care units (ICUs) for a wide variety of reasons (1–3). Some reasons are related to clinical issues related directly to HIV infection, such as opportunistic infections. Health care professionals should recognize that these patients also become hospitalized for the same reasons that HIV-uninfected patients are admitted (i.e., for HIV-unrelated issues, such as trauma, acute infections, chronic pulmonary disease, chronic coronary artery disease, etc.). These latter patients need the same management strategies as HIV-uninfected patients with a few exceptions. In this country, health care professionals have long since discarded the flawed notion that HIV-infected patients should be managed differently solely based on their HIV status, rather than on the basis of their clinical conditions and personal preferences. There are, however, some special differences for HIV-infected patients. First, if they are receiving antiretroviral agents, a decision must be made whether to continue the drugs in the hospital (*see below*) or whether to discontinue them. Second, certain antiretroviral drugs have profound drug–drug interactions that must be considered when prescribing other agents whose pharmacokinetics might be substantially affected. Third, health care providers need to be cognizant that there is nosocomial exposure to percutaneous or musosal fluids that might be HIV infected; they must take appropriate preventive steps to reduce the likelihood of occupational HIV transmission.

This article focuses on patients admitted to the ICU for conditions related to their HIV status.

EPIDEMIOLOGY

Since the introduction of more potent antiretroviral agents in the mid-1990s, it has been apparent to all clinicians that the frequency of opportunistic infections has declined, and patient survival has increased (4). The decline in opportunistic infections has been uniform; that is, all infectious complications have decreased in incidence. However, some neoplastic complications have not been affected in the same manner (5–10). Although Kaposi's sarcoma and primary central nervous system (CNS) lymphoma have declined dramatically in incidence, the incidence of nonprimary CNS B-cell lymphoma has been stable, and may be increasing in terms of lifetime risk as patients live longer. In addition, it is becoming apparent that unusual tumors linked to human herpesvirus 8 (HHV-8) are increasing, such as multicentric Castleman's disease and primary effusion cell lymphoma (11–15). Solid tumors may also be increasing, such as bronchogenic carcinoma, melanoma, and renal cell carcinoma, although more data are needed to confirm these initial observations (16, 17).

As opportunistic infections have declined, the causes for hospitalization have changed. The proportion of hospitalizations due to respiratory diseases is still considerable, but has been falling (18). The proportion of hospitalizations due to hepatic disease (especially sequelae of hepatitis C), renal disease (consequences of HIV nephropathy and other disorders), and cardiovascular disease has increased. Among pulmonary complications, the incidence of pneumocystis pneumonia (PCP) has declined, and the fraction of PCP cases that require hospitalization, or admission to the ICU, is falling. Thus, the face of HIV infection in the hospital and in the ICU has changed over the past decade.

Although the face of the HIV epidemic is changing in the United States and Western Europe, clinicians must recognize that there are two distinct populations of patients. First, there are patients with access to care and to the full armamentarium of HIV-related drugs. For these patients, survival is longer and opportunistic complications are fewer, as noted above. These patients are more likely to be admitted to the ICU for non–HIV-related problems, or for complications of their HIV drugs. These patients may eventually lose their responsiveness to antiretroviral therapy (ART), but with opportunistic infection prophylaxis, and perhaps with continuation of ART, they appear to have fewer infectious complications.

In contrast to this patient population is the sizable number of individuals in the United States who are either unaware of their HIV status or who lack access to care. These patients continue to appear in emergency rooms and physician offices with the same opportunistic infections that were seen in the

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1980s. The management of these infections has recently been summarized in the National Institutes of Health/Centers of Disease Control and Prevention/Infectious Diseases Society of America Guidelines on Treatment of Opportunistic Infections in HIV-infected Persons (www.aidsinfo.nih.gov) (19).

DIFFERENTIAL DIAGNOSIS: THE USE OF LABORATORY MARKERS

When a patient with HIV infection presents to a health care provider, it is important to recognize that the patient may or may not have an HIV-related problem. Clinicians often assume that such patients have an opportunistic infection, neoplastic problem, or metabolic disorder that is related to HIV infection, yet such patients are also at risk for common processes. Even if the patient is infected, the infectious process may be caused by a common community-acquired pathogen, and not by an opportunistic pathogen.

$CD4^+$ T-lymphocyte counts continue to be excellent indicators of the susceptibility of patients to HIV-related opportunistic infections. ART has not altered the relationship of $CD4^+$ T-cell counts to the occurrence of opportunistic infections that was established in the pre-ART era (19). Any differences in counts between patients on ART and off ART are minimal and have no diagnostic significance. In addition, the nadir $CD4^+$ T-lymphocyte count has little clinical implication about susceptibility to opportunistic infections. The key parameter is the current $CD4^+$ T-lymphocyte count, not the nadir count from the past. There are subtle differences in immunologic function based on nadir count that can be dissected by laboratory evaluations, but it is not clear that these differences have major clinical implications (20).

Viral load is predictive of the occurrence of opportunistic infections. Detectable viral loads do correlate with immune activation and decreased response to specific pathogens. Thus, a patient with a given $CD4^+$ T-lymphocyte count who has a high viral load appears to be at enhanced risk for an AIDS-defining illness than a patient with a comparable $CD4^+$ T-lymphocyte count and a low viral load, but this difference is difficult to measure.

Other parameters predict susceptibility to opportunistic processes. The plasma cytomegalovirus (CMV) viral load correlates with susceptibility; that is, those with high CMV viral loads are at higher risk than those with viral loads below the limit of detection (21). Whether this correlation is due to a direct effect of CMV on immune function or whether this is a marker for poor immune control of pathogens in general is not clear. Clinical parameters are important prognostically. A patient with a $CD4^+$ T-cell count higher than 200 cells/μl who develops oral thrush, or PCP, or bacterial pneumonia is at higher risk for developing another opportunistic infection compared with a patient with the same $CD4^+$ T-cell count who has not had one of those complications. This observation has implications for differential diagnosis of subsequent syndromes and for initiating prophylaxis.

ART IN THE ICU

When HIV-infected patients are admitted to the ICU, a major issue is whether to continue their ART or stop the drugs (19). Intensivists need to be aware of several important principles. First, antiretroviral agents are only available as oral tablets and suspensions, for the most part. Zidovudine and enfuvirtide are the only agents available in parenteral form. Thus, the pharmacokinetics of ART will be unpredictable in severely ill patients, with uncertain gastrointestinal absorption and potential drug interactions. Second, protease inhibitors and nonnucleoside reverse transcriptase inhibitors are metabolized by the cytochrome p-450 enzyme system. They will alter the metabolism of other drugs metabolized by this system, and they themselves will have their pharmacokinetics altered (22, 23). This can produce drug toxicities if serum levels of drugs are augmented, and lack of efficacy if drug levels are reduced.

For ART, even a few days of suboptimal levels due to poor absorption or pharmacokinetic interactions can have disastrous results (i.e., irreversible drug resistance can occur). Thus, in most situations, the best strategy is to stop all ART during the ICU admission, and to consult an experienced pharmacokineticist about the effects on drug metabolism even after ART has been stopped (19). Stopping ART is unlikely to lead to drug resistance: $CD4^+$ T-cell counts may fall, but that is a less serious consequence than producing drug resistance. Stopping nonnucleoside reverse transcriptase inhibitors can be complicated pharmacologically: the advice of an experienced pharmacist or infectious disease specialist can facilitate development of the optimal management strategy that will not induce resistance due to the longer half-life of the nonnucleoside reverse transcriptase inhibitor compared with the other drugs.

Third, drug toxicities are often difficult to attribute to a specific drug. Thus, when ART is added to a regimen and potential toxicities such as rash, liver function test abnormalities, or elevated amylase level occur, it is difficult to know whether to attribute the toxicity to the ART or to another drug or disease process. Thus, discontinuing ART simplifies management of clinical issues that could potentially be due to ART.

The initiation of ART for patients in the ICU can cause immune reconstitution syndromes (IRS). These can be life threatening and difficult to distinguish from other clinical syndromes, as described below. Thus, there is yet another reason to be reluctant to initiate ART in the ICU.

PULMONARY DISEASE

Bacterial Infections

Patients with HIV infection are well recognized as candidates to develop pulmonary disease due to a wide array of opportunistic and nonopportunistic processes (24–26). Clinicians should recognize that *Streptococcus pneumoniae* continues to be the most common cause of upper and lower respiratory disease in this patient population. Patients have an increased incidence of bacterial respiratory infections at all $CD4^+$ T-cell strata, although the incidence does increase as the $CD4^+$ T-cell count declines (26). *Haemophilus influenzae*, both the encapsulated and nonencapsulated types, is also common. There is a growing literature about the occurrence of pneumonia due to *Staphylococcus aureus*, especially oxacillin-resistant strains, and about *Pseudomonas aeruginosa*, especially among patients with low $CD4^+$ T-cell counts (27, 28). However, *S. pneumoniae* and *H. influenzae* continue to be the predominant organisms.

The clinical presentation, diagnosis, and therapy for bacterial pneumonia do not differ substantially for HIV-infected patients compared with HIV-uninfected patients. Bacteremia and extrapulmonary disease appear to be more common, at least for *S. pneumoniae*.

Mycobacterial Infections

In most parts of the world, *Mycobacterium tuberculosis* is a major cause of pulmonary and extrapulmonary disease in patients with HIV infection (29, 30). In contrast, in the United States and Western Europe, tuberculosis is relatively uncommon except among immigrants and individuals with special exposures, such as those residing or working in correctional facilities. Tuberculosis must be a consideration for every patient who presents with

pulmonary disease both to facilitate appropriate therapy and to prevent transmission to health care workers, patients, and visitors.

The recognition and management of tuberculosis is a complex process that, unlike the other bacterial diseases above, has many differences in recognition and management in HIV-uninfected patients (31). Tuberculosis presents in many typical and atypical forms both for pulmonary and extrapulmonary manifestations. When patients have a potential exposure and present with febrile illnesses, tuberculosis should always be a consideration given the major predisposition HIV-infected patients to develop disease once patients are infected. The likelihood of disease is estimated to be 10% per year, as opposed to 10% per lifetime for HIV-uninfected individuals.

Treatment of tuberculosis is complicated by the drug interactions of ART agents and antituberculous agents (19, 31, 32). Rifampin, in particular, has complex interactions with the protease inhibitors and nonnucleoside reverse transcriptase inhibitors. ART agents and antituberculous drugs also have overlapping toxicities, especially liver adverse events. There are guidelines recommending the appropriate dose and drug adjustments to be made to standard regimens (19).

Treatment of tuberculosis is also complicated by the occurrence of IRS (32–37). These syndromes will be discussed below. Such syndromes associated with recent tuberculosis can be clinically severe and can make initiation of ART a much more complicated endeavor in regions where tuberculosis is common.

Although *M. tuberculosis* occurs with enhanced frequency in patients with HIV infection, the paucity of cases of pulmonary disease due to *Mycobacterium avium* complex stands in marked contrast. *M. avium* complex clearly causes considerable morbidity in this patient population when patients have $CD4^+$ T-cell counts below 50 to 75 cells/μl. However, disease almost always manifests as mycobacteremia, lymphadenitis, or enteritis. Although the lung may be colonized with *M. avium* (i.e., *M. avium* may be readily found in pulmonary secretions), this organism is almost never the cause of pulmonary dysfunction (19). There are a few documented cases, but in most instances, tissue is needed to be certain that another process is not causing the pulmonary dysfunction.

Other mycobacteria occasionally cause pulmonary disease in patients with HIV infection. *Mycobacterium kansasii* is probably the most common. However, no mycobacteria other than *M. tuberculosis* occurs with great frequency as a cause of significant lung pathology.

Pneumocystis jiroveci

Pneumocystis jiroveci (abbreviated PCP to indicate pneumocystis pneumonia) continues to be a common cause of pulmonary disease in the United States and Western Europe (2, 3, 19). PCP occurs in developing countries, although its frequency in those settings is uncertain. Whether the pathogen is less common in those areas, or whether PCP is underdiagnosed, or whether patients die before the onset of PCP due to other disease processes is unclear.

PCP occurs in the United States predominantly in patients who are not receiving either ART or anti–pneumocystis prophylaxis. As indicated above, the outcome of patients with PCP has improved over the past decade. Clinicians are more aware of this entity at $CD4^+$ T-cell counts below 200 cells/μl, and diagnosis has improved with the more widespread availability of induced sputum examination and immunofluorescent antibody staining to supplement bronchoalveolar lavage and transbronchial lung biopsy stained with methenamine silver or Giemsa. Clinicians need to be cognizant, however, that about 10 to 15% of cases of PCP occur at $CD4^+$ T-cell counts higher than 200 cells/μl (38). Thus, when patients present with pulmonary processes at $CD4^+$ T-cell counts greater than 200 cells/μl, PCP should usually not be the first diagnosis considered, but it should not be excluded from the differential diagnosis.

PCP usually presents as a subacute illness over several weeks, and the chest radiograph typically demonstrates bilateral, symmetric interstitial infiltrates (39). However, atypical presentations are not uncommon: PCP has been documented to produce lobar infiltrates, nodules, cavities, and effusions. Thus, empiric diagnoses on the basis of clinical presentation are less desirable than specific diagnoses on the basis of direct microscopy, culture, or some type of antigen or nucleic acid detection to be certain that the correct pathogen is being treated, and that toxicities of unnecessary drugs are avoided.

Extrapulmonary PCP also occurs in patients with HIV infection. Lesions in the liver and spleen are probably most common. However, lesions in the kidneys, brain, eye, and lymph nodes have also been seen. Distributive shock has also been reported in association with PCP.

The therapy of choice for PCP continues to be trimethoprim–sulfamethoxazole (TMP-SMX); prednisone should be added to patients who present with room air Po_2 of less than 70 mm Hg. There is molecular evidence that mutations likely to confer sulfonamide resistance are occurring with growing frequency among HIV-infected patients (40–43). Because the sulfa component of TMP-SMX is probably the only active agent in this compound against PCP, such resistance could become a major management problem. However, there is no clear consensus from published trials that this resistance alters patient outcome, although several studies have suggested such an effect.

For patients who cannot tolerate TMP-SMX or who fail this drug, the most effective alternative is intravenous pentamidine. This drug is well known for its toxicities, which include renal impairment, dysglycemias, and pancreatitis. Dapsone–trimethoprim is effective, but this combination is only available in oral form, and the dapsone cross-reacts with sulfamethoxazole in approximately 50% of patients. Thus, this combination offers only modest breadth to the anti-PCP armamentarium. Clindamycin plus primaquine, atovaquone, and trimetrexate are other options. Of these, only trimetrexate can be administered parenterally; that is, there is no parenteral form of atovaquone or primaquine.

Fungal Pneumonia

Fungal pneumonias (other than PCP) occur in patients with HIV infection, but they are not common in most geographic areas. Cryptococcus, histoplasma, and coccidioides are all recognized to cause focal or diffuse pulmonary disease. In general, focal disease is more common among patients with higher $CD4^+$ T-cell counts, and diffuse disease is more frequent among patients with $CD4^+$ T-lymphocyte counts lower than 200 cells/μl.

Diagnosis and therapy of these pneumonias do not differ substantially from that for disease in other immunosuppressed patients. When these pneumonias occur in patients with low $CD4^+$ T-lymphocyte counts, they are difficult to distinguish clinically from PCP. This reinforces the desirability of establishing a specific diagnosis when patients with HIV infection present with pulmonary pathology. For patients with disease and $CD4^+$ T-cell counts less than 200 cells/μl, therapy must usually be continued throughout life unless immunity is reconstituted by ART.

Aspergillus has been reported as a cause of tracheobronchial or pulmonary disease with increasing frequency (44). Patients typically have either a low $CD4^+$ T-cell count or neutropenia. Not all patients have the latter. The diagnosis may be established by the bronchoscopist who recognizes a characteristic plaquelike lesion in the bronchus that is smear- and culture-positive for

aspergillus. How well these patients will survive with early diagnosis and combination fungal therapies remains to be determined.

Viral Pneumonia

Interestingly, the herpesviruses have not been common causes of pulmonary dysfunction in patients with HIV. CMV is often found in respiratory secretions when patients have low $CD4^+$ T-lymphocyte counts, but CMV is rarely the cause of pulmonary dysfunction. Studies have shown, for instance, that the prevalence of CMV in respiratory secretions correlates inversely with the $CD4^+$ T-lymphocyte count. It has also been shown that when CMV was present in the lung biopsies of patients with PCP, patients did as well with anti-PCP therapy alone as did patients who had no such inclusions. Thus, to document CMV as the cause of pulmonary dysfunction in this patient population requires tissue demonstrating multiple inclusion bodies and the absence of another likely pathogen.

Herpes simplex virus and varicella-zoster virus have been described as causing pulmonary disease in this patient population. However, this is usually in the setting of disseminated disease when lesions in the skin are apparent. Some cases of herpes simplex virus pneumonia appear to be extensions from the oropharynx, but such cases are unusual in this patient population.

Influenza, respiratory syncytial virus, adenovirus, and coronavirus all cause pulmonary disease in this patient population. However, there is no evidence that these viruses cause disease with any increased frequency or virulence in this patient population. Thus, they are not considered to be HIV-associated opportunistic infections.

IRS

When ART is initiated in patients with HIV infection and a drug-sensitive virus, immune function improves as the viral load is reduced and the $CD4^+$ T-cell count increases. This improved immunologic responsiveness often manifests as organ dysfunction in response to latent or apparent antigens that can range from mild and clinically unimportant to severe and life threatening.

IRS have been described in case series (19, 32–36, 45–49). There are few well-constructed studies defining the immunologic correlates, or the factors that predict their occurrence. From the observational studies published to date, it would appear that the syndrome is most likely to occur in patients who started ART when their $CD4^+$ T-cell count is low, typically less than 100 cells/μl, and when their viral load is high, typically greater than 100,000 copies/μl. The IRS occurs within weeks or months of starting ART: some syndromes can occur within days, and others, as described below, may not manifest for many months or several years. Because immune function improves qualitatively as soon as the viral load falls, some patients with IRS may not manifest a higher $CD4^+$ T-lymphocyte count at the time of the IRS. Alternatively, some patients with organisms in a sequestered focus, such as bone, are more likely to have the late manifestations. These IRS appear to be most common in areas where tuberculosis or cryptococcosis is common.

The relationship of IRS to specific pathogens is being defined. Some experts report, for instance, that IRS rarely occurs due to latent *M. tuberculosis*, but commonly occurs due to latent *M. avium* complex. IRS commonly occurs after active tuberculosis is diagnosed. For CMV retinitis, IRS can occur weeks, months, or years after the CMV retinitis is stabilized by drug therapy if ART is belatedly initiated.

There is no consensus case definition of IRS, and thus the literature includes reports that categorize clinical manifestations differently. It is extremely difficult when a patient presents with a new clinical syndrome after starting IRS to determine if the manifestation is an immunologic reaction that needs no specific intervention, or whether the process represents an active opportunistic infection in need of therapy. Some series include patients with fungemia or mycobacteremia as examples of IRS. Other series would include such patients as cases of active or new opportunistic infections in need of specific therapy. These uncertainties leave the clinician with a dilemma about how aggressive to be diagnostically or therapeutically.

Some syndromes have been managed without therapy. Some syndromes that were clinically more severe have been treated with antiinflammatory agents, including prednisone. Other syndromes have been treated with long courses of specific antiinfective therapy. At this juncture, there is no evidence on which to base a recommendation for the optimal approach.

NEOPLASTIC DISEASE

Kaposi's sarcoma and lymphoma are well-recognized causes of pulmonary disease in patients with HIV infection (10, 50–54). The incidence of Kaposi's sarcoma has declined as the epidemic has moved into heterosexual individuals and women, groups that do not characteristically have a high incidence of Kaposi's sarcoma. In addition, ART use has been associated with a decline in this tumor, which is linked to HHV-8 infection.

When Kaposi's sarcoma does occur in the lung, it presents as patchy bronchial lesions (51–54). Often, there is an associated pleural effusion that is bloody when thoracentesis is performed. The diagnosis is often anticipated by concurrent skin lesions and the presence of prominent lesions in the tracheobronchial tree, which are easily recognized by bronchoscopy. The diagnosis is not easy to establish definitively. Transbronchial biopsies of the bronchus or lung parenchyma reveal crush artifact that is hard to distinguish from Kaposi's sarcoma. On cytology, there is no diagnostic feature. Thus, either tissue must be obtained on open lung biopsy or video-assisted thoracoscopy, or a presumptive diagnosis must be made when Kaposi's sarcoma in seen in the tracheobronchial tree and bronchoalveolar lavage reveals no other likely pathogens.

Pulmonary Kaposi's sarcoma can respond well to chemotherapy (55–58). The use of ART and opportunistic infection prophylaxis has contributed to the success rates of management strategies.

Lymphoma continues to be a cause of pulmonary disease (54, 59, 60). Although primary CNS lymphomas have greatly diminished in frequency in patients treated with ART, primary B-cell lymphomas elsewhere continue to occur. Patchy pulmonary infiltrates have been well described. Biopsy or cytology is needed to establish a diagnosis (10, 54).

Combination chemotherapy for HIV-associated lymphoma has become impressively more successful when ART is continued with opportunistic infection prophylaxis (61–63). Some regimens provide a brief drug holiday while the patients is actively receiving chemotherapy to avoid problems with drug absorption or drug interactions. However, it would appear that active ART and opportunistic infection prophylaxis are important elements contributing to improved survival. Stem cell transplantation has also been used successfully (63–65).

As patients have lived longer, and experience with large patient numbers has increased, other pulmonary neoplastic processes have been recognized that clinicians should be aware of. Primary effusion cell lymphoma can present in the pleural, pericardial, or abdominal cavities, and presents as effusions. This HHV-8– and Epstein-Barr virus–associated tumor is diagnosed by cytology in many cases. It is not clear how effective chemotherapy is for this tumor.

Multicentric Castleman's disease is another unusual neoplastic process that is associated with HIV infection (11, 14, 66). This HHV-8 process can present with pulmonary infiltrates, as well as fever, lethargy, adenopathy, and cytopenias. Diagnosis usually requires a combination of HHV-8 titers and bone marrow or lymph node tissue, plus flow cytometry (11, 14, 66, 67). Patients often develop lymphoma and/or Kaposi's sarcoma subsequently. It is unclear how effective any therapy is for this disease.

Several large databases have suggested that certain solid tumors can be overrepresented in this patient population (7, 16, 17, 68, 69). Bronchogenic carcinoma as well as melanoma, colon cancer, and breast cancer appear to occur with increased frequency even when other risk factors are considered.

PREMATURE ATHEROSCLEROSIS

Clinicians must recognize that patients with HIV infection have accelerated atherosclerosis (1). It is not clear what role HIV itself has; however, ART could conceivably have a direct toxic effect on endothelial cells, or could accelerate atherosclerosis by its effects on insulin resistance and lipid profiles. However, as patients present with pulmonary syndromes, clinicians must consider ischemic heart disease and congestive heart failure in their differential diagnosis. In addition, as the HIV-infected population ages, age-appropriate atherosclerosis will be increasingly recognized and must be managed in the setting of HIV care.

DRUG TOXICITIES

Several antiretroviral agents have toxicities that can present with pulmonary or respiratory manifestations.

When patients receive ART regimens that contain abacavir, they can develop a hypersensitivity syndrome that is difficult to distinguish from nonspecific febrile respiratory illnesses (70–73). However, because abacavir hypersensitivity reactions can be fatal, this syndrome must be recognized.

Patients present during the initial 4 to 8 wk of abacavir therapy with fever, rash, fatigue, nausea, or vomiting. About 20% of patients will have cough; some of these patients have been described to have pulmonary infiltrates. The syndrome usually persists unless the drug is discontinued. A feature that clinicians must be aware of is the danger of "rechallenge." Patients with this syndrome may stop taking their drugs due to their systemic illness, or their nausea and vomiting. Cases of distributive shock, some fatal, have occurred on rechallenge. Thus, most experts would recommend that if a potential syndrome occurs, and the drug is discontinued, rechallenge should not be permitted. There is a link between abacavir hypersensitivity syndrome and HLA B27, but it is not clear yet whether screening patients for this genotype would be cost-effective.

Another drug toxicity that can present with dyspnea occurs when patients have been receiving nucleoside antiretroviral agents for long periods of time (74). Any of the nucleosides (zidovudine, stavudine, didanosine, lamivudine, abacavir, emtricitabine) can probably cause this syndrome, although it is best described with didanosine and stavudine. This syndrome is a reflection of mitochondrial toxicity. Patients with this syndrome are often female and obese. Hepatic steatosis is frequently associated with the disease. Patients present with weakness and fatigue, and eventually develop lactic acidosis. Serum lactate levels are typically considerably above 5 mmol/μl. These patients may appear to be septic, although they are not usually febrile. The only effective therapy is to stop the drug: other interventions, such as carnitine or riboflavin, have no documented benefit. Whether patients can subsequently be safely rechallenged with other nucleosides has not been well studied, although abacavir, lamivudine, and FTC seem to impart very little risk.

CONCLUSIONS

The clinical features of patients with HIV infection who present to ICUs have changed over the past 25 yr. As patients with HIV infection live longer, more are being seen in ICUs for issues unrelated to their HIV infection. When they are admitted to the ICU, for whatever reasons, intensivists need to be knowledgeable about the complex issues related to efficacy and toxicities of ART. New manifestations, such as IRS and premature atherosclerosis, are emerging. HIV-infected patients in the ICU are clearly a population that requires special expertise for optimal management.

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References

1. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiebaut R, Morfeldt L, De Wit S, Pradier C, *et al.* Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003;349:1993–2003.
2. Morris A, Creasman J, Turner J, Luce JM, Wachter RM, Huang L. Intensive care of human immunodeficiency virus-infected patients during the era of highly active antiretroviral therapy. *Am J Respir Crit Care Med* 2002;166:262–267.
3. Morris A, Huang L. Intensive care of patients with HIV infection: HAART warming improvement but beware of future HAART (and heart) attacks. *Chest* 2004;125:1602–1604.
4. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338: 853–860.
5. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, *et al.* Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005;97:425–432.
6. Cooksley CD, Hwang LY, Waller DK, Ford CE. HIV-related malignancies: community-based study using linkage of cancer registry and HIV registry data. *Int J STD AIDS* 1999;10:795–802.
7. Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. Risk of cancer in people with AIDS. *AIDS* 1999;13:839–843.
8. Mocroft A, Kirk O, Clumeck N, Gargalianos-Kakolyris P, Trocha H, Chentsova N, Antunes F, Stellbrink HJ, Phillips AN, Lundgren JD. The changing pattern of Kaposi sarcoma in patients with HIV, 1994–2003: the EuroSIDA Study. *Cancer* 2004;100:2644–2654.
9. Parker MS, Leveno DM, Campbell TJ, Worrell JA, Carozza SE. AIDS-related bronchogenic carcinoma: fact or fiction? *Chest* 1998;113:154–161.
10. Scadden DT. AIDS-related malignancies. *Annu Rev Med* 2003;54: 285–303.
11. Aaron L, Lidove O, Yousry C, Roudiere L, Dupont B, Viard JP. Human herpesvirus 8-positive Castleman disease in human immunodeficiency virus-infected patients: the impact of highly active antiretroviral therapy. *Clin Infect Dis* 2002;35:880–882.
12. Boulanger E, Gerard L, Gabarre J, Molina JM, Rapp C, Abino JF, Cadranel J, Chevret S, Oksenhendler E. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. *J Clin Oncol* 2005;23:4372–4380.
13. Lim ST, Rubin N, Said J, Levine AM. Primary effusion lymphoma: successful treatment with highly active antiretroviral therapy and rituximab. *Ann Hematol* 2005;84:551–552.
14. Oksenhendler E, Duarte M, Soulier J, Cacoub P, Welker Y, Cadranel J, Cazals-Hatem D, Autran B, Clauvel JP, Raphael M. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS* 1996;10:61–67.
15. Simonelli C, Spina M, Cinelli R, Talamini R, Tedeschi R, Gloghini A, Vaccher E, Carbone A, Tirelli U. Clinical features and outcome of primary effusion lymphoma in HIV-infected patients: a single-institution study. *J Clin Oncol* 2003;21:3948–3954.

16. Bower M, Powles T, Nelson M, Shah P, Cox S, Mandelia S, Gazzard B. HIV-related lung cancer in the era of highly active antiretroviral therapy. *AIDS* 2003;17:371–375.
17. Herida M, Mary-Krause M, Kaphan R, Cadranel J, Poizot-Martin I, Rabaud C, Plaisance N, Tissot-Dupont H, Boue F, Lang JM, *et al.* Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol* 2003;21:3447–3453.
18. Grubb JR, Moorman AC, Baker RK, Masur H. The changing spectrum of pulmonary disease in patients with HIV infection on anti-retroviral therapy. *AIDS* (In press)
19. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. *MMWR Morb Mortal Wkly Rep* 2004;53(RR-4):1–33.
20. Miller V, Mocroft A, Reiss P, Katlama C, Papadopoulos AI, Katzenstein T, van Lunzen J, Antunes F, Phillips AN, Lundgren JD. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study. *Ann Intern Med* 1999;130:570–577.
21. Spector SA, Wong R, Hsia K, Pilcher M, Stempien MJ. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. *J Clin Invest* 1998;101:497–502.
22. Boffito M, Acosta E, Burger D, Fletcher CV, Flexner C, Garaffo R, Gatti G, Kurowski M, Perno CF, Peytavin G, *et al.* Therapeutic drug monitoring and drug-drug interactions involving antiretroviral drugs. *Antivir Ther* 2005;10:469–477.
23. Flexner C, Piscitelli SC. Drug administration and interactions. In: Dolin R, Masur H, Saag MS, editors. AIDS therapy, 2nd ed. Philadelphia: Churchill-Livingstone; 2003. pp. 923–939.
24. Dufour V, Cadranel J, Wislez M, Lavole A, Bergot E, Parrot A, Rufat P, Mayaud C. Changes in the pattern of respiratory diseases necessitating hospitalization of HIV-infected patients since the advent of highly active antiretroviral therapy. *Lung* 2004;182:331–341.
25. McKenzie R, Travis WD, Dolan SA, Pittaluga S, Feuerstein IM, Shelhamer J, Yarchoan R, Masur H. The causes of death in patients with human immunodeficiency virus infection: a clinical and pathologic study with emphasis on the role of pulmonary diseases. *Medicine (Baltimore)* 1991;70:326–343.
26. Wallace JM, Hansen NI, Lavange L, Glassroth J, Browdy BL, Rosen MJ, Kvale PA, Mangura BT, Reichman LB, Hopewell PC. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med* 1997;155:72–80.
27. Allen SH, Brennan-Benson P, Nelson M, Asboe D, Bower M, Azadian B, Gazzard B, Stebbing J. Pneumonia due to antibiotic resistant Streptococcus pneumoniae and Pseudomonas aeruginosa in the HAART era. *Postgrad Med J* 2003;79:691–694.
28. Mathews WC, Caperna JC, Barber RE, Torriani FJ, Miller LG, May S, McCutchan JA. Incidence of and risk factors for clinically significant methicillin-resistant Staphylococcus aureus infection in a cohort of HIV-infected adults. *J Acquir Immune Defic Syndr* 2005;40:155–160.
29. Kirk O, Gatell JM, Mocroft A, Pedersen C, Proenca R, Brettle RP, Barton SE, Sudre P, Phillips AN. Infections with Mycobacterium tuberculosis and Mycobacterium avium among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group JD. *Am J Respir Crit Care Med* 2000;162:865–872.
30. Lawn SD, Badri M, Wood R. Risk factors for tuberculosis among HIV-infected patients receiving antiretroviral treatment. *Am J Respir Crit Care Med* 2005;172:1348.
31. Gordin F. *Mycobacterium tuberculosis* infection. In: Dolin R, Masur H, Saag MS, editors. AIDS therapy, 2nd ed. Philadelphia: Churchill-Livingstone; 2003. pp. 456–474.
32. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, Fisher M, Taylor GP, Miller R, Taylor CB, *et al.* Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002;16:75–83.
33. Breen RA, Smith CJ, Bettinson H, Dart S, Bannister B, Johnson MA, Lipman MC. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004;59:704–707.
34. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther* 2005;10:417–422.
35. Navas E, Martin-Davila P, Moreno L, Pintado V, Casado JL, Fortun J, Perez-Elias MJ, Gomez-Mampaso E, Moreno S. Paradoxical reactions of tuberculosis in patients with the acquired immunodeficiency syndrome who are treated with highly active antiretroviral therapy. *Arch Intern Med* 2002;162:97–99.
36. Shelburne SA III, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Musher DW, Gathe JC Jr, Visnegarwala F, Trautner BW. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine (Baltimore)* 2002;81:213–227.
37. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White AC Jr, Hamill RJ. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005;19:399–406.
38. Chu SY, Hanson DL, Ciesielski C, Ward JW. Prophylaxis against Pneumocystis carinii pneumonia at higher CD4+ T-cell counts. *JAMA* 1995;273:848.
39. Thomas CF Jr, Limper AH. Pneumocystis pneumonia. *N Engl J Med* 2004;350:2487–2498.
40. Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. Effects of mutations in Pneumocystis carinii dihydropteroate synthase gene on outcome of AIDS-associated P. carinii pneumonia. *Lancet* 1999;354:1347–1351.
41. Huang L, Crothers K, Atzori C, Benfield T, Miller R, Rabodonirina M, Helweg-Larsen J. Dihydropteroate synthase gene mutations in Pneumocystis and sulfa resistance. *Emerg Infect Dis* 2004;10:1721–1728.
42. Ma L, Kovacs JA, Cargnel A, Valerio A, Fantoni G, Atzori C. Mutations in the dihydropteroate synthase gene of human-derived Pneumocystis carinii isolates from Italy are infrequent but correlate with prior sulfa prophylaxis. *J Infect Dis* 2002;185:1530–1532.
43. Stein CR, Poole C, Kazanjian P, Meshnick SR. Sulfa use, dihydropteroate synthase mutations, and Pneumocystis jirovecii pneumonia. *Emerg Infect Dis* 2004;10:1760–1765.
44. Mylonakis E, Barlam TF, Flanigan T, Rich JD. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest* 1998;114:251–262.
45. Dean GL, Williams DI, Churchill DR, Fisher MJ. Transient clinical deterioration in HIV patients with Pneumocystis carinii pneumonia after starting highly active antiretroviral therapy: another case of immune restoration inflammatory syndrome. *Am J Respir Crit Care Med* 2002;165:1670. [Author reply, 1670.]
46. Fishman JE, Saraf-Lavi E, Narita M, Hollender ES, Ramsinghani R, Ashkin D. Pulmonary tuberculosis in AIDS patients: transient chest radiographic worsening after initiation of antiretroviral therapy. *AJR Am J Roentgenol* 2000;174:43–49.
47. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998;158:157–161.
48. Phillips P, Bonner S, Gataric N, Bai T, Wilcox P, Hogg R, O'Shaughnessy M, Montaner J. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis* 2005;41:1483–1497.
49. Wislez M, Bergot E, Antoine M, Parrot A, Carette MF, Mayaud C, Cadranel J. Acute respiratory failure following HAART introduction in patients treated for Pneumocystis carinii pneumonia. *Am J Respir Crit Care Med* 2001;164:847–851.
50. Aboulafia DM. The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma. *Chest* 2000;117:1128–1145.
51. Cadranel JL, Kammoun S, Chevret S, Parrot A, Denis M, Winter C, Carette MF, Rozenbaum W, Akoun GM, Mayaud CM. Results of chemotherapy in 30 AIDS patients with symptomatic pulmonary Kaposi's sarcoma. *Thorax* 1994;49:958–960.
52. Hartman TE, Primack SL, Muller NL, Staples CA. Diagnosis of thoracic complications in AIDS: accuracy of CT. *AJR Am J Roentgenol* 1994;162:547–553.
53. Huang L, Schnapp LM, Gruden JF, Hopewell PC, Stansell JD. Presentation of AIDS-related pulmonary Kaposi's sarcoma diagnosed by bronchoscopy. *Am J Respir Crit Care Med* 1996;153:1385–1390.
54. Tirelli U, Spina M, Gaidano G, Vaccher E, Franceschi S, Carbone A. Epidemiological, biological and clinical features of HIV-related lymphomas in the era of highly active antiretroviral therapy. *AIDS* 2000;14:1675–1688.
55. Dupin N, Rubin De Cervens V, Gorin I, Calvez V, Pessis E, Grandadam M, Rabian C, Viard JP, Huraux JM, Escande JP. The influence of highly active antiretroviral therapy on AIDS-associated Kaposi's sarcoma. *Br J Dermatol* 1999;140:875–881.
56. Holkova B, Takeshita K, Cheng DM, Volm M, Wasserheit C, Demopoulos R, Chanan-Khan A. Effect of highly active antiretroviral therapy on survival in patients with AIDS-associated pulmonary Kaposi's sarcoma treated with chemotherapy. *J Clin Oncol* 2001;19:3848–3851.

57. Lichterfeld M, Qurishi N, Hoffmann C, Hochdorfer B, Brockmeyer NH, Arasteh K, Mauss S, Rockstroh JK. Treatment of HIV-1-associated Kaposi's sarcoma with pegylated liposomal doxorubicin and HAART simultaneously induces effective tumor remission and CD4+ T cell recovery. *Infection* 2005;33:140–147.
58. Martin-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R, Valencia ME, Alegre M, Podzamczer D, Gonzalez-Lahoz J. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. *AIDS* 2004;18:1737–1740.
59. Bazot M, Cadranel J, Benayoun S, Tassart M, Bigot JM, Carette MF. Primary pulmonary AIDS-related lymphoma: radiographic and CT findings. *Chest* 1999;116:1282–1286.
60. Eisner MD, Kaplan LD, Herndier B, Stulbarg MS. The pulmonary manifestations of AIDS-related non-Hodgkin's lymphoma. *Chest* 1996;110: 729–736.
61. Little RF, Pittaluga S, Grant N, Steinberg SM, Kavlick MF, Mitsuya H, Franchini G, Gutierrez M, Raffeld M, Jaffe ES, *et al.* Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood* 2003;101:4653–4659.
62. Ratner L, Lee J, Tang S, Redden D, Hamzeh F, Herndier B, Scadden D, Kaplan L, Ambinder R, Levine A, *et al.* Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. *J Clin Oncol* 2001;19: 2171–2178.
63. Re A, Cattaneo C, Michieli M, Casari S, Spina M, Rupolo M, Allione B, Nosari A, Schiantarelli C, Vigano M, *et al.* High-dose therapy and autologous peripheral-blood stem-cell transplantation as salvage treatment for HIV-associated lymphoma in patients receiving highly active antiretroviral therapy. *J Clin Oncol* 2003;21:4423–4427.
64. Krishnan A, Molina A, Zaia J, Smith D, Vasquez D, Kogut N, Falk PM, Rosenthal J, Alvarnas J, Forman SJ. Durable remissions with autologous stem cell transplantation for high-risk HIV-associated lymphomas. *Blood* 2005;105:874–878.
65. Serrano D, Carrion R, Balsalobre P, Miralles P, Berenguer J, Buno I, Gomez-Pineda A, Ribera JM, Conde E, Diez-Martin JL. HIV-associated lymphoma successfully treated with peripheral blood stem cell transplantation. *Exp Hematol* 2005;33:487–494.
66. Hillier JC, Shaw P, Miller RF, Cartledge JD, Nelson M, Bower M, Francis N, Padley SP. Imaging features of multicentric Castleman's disease in HIV infection. *Clin Radiol* 2004;59:596–601.
67. Oksenhendler E, Carcelain G, Aoki Y, Boulanger E, Maillard A, Clauvel JP, Agbalika F. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. *Blood* 2000;96:2069–2073.
68. Braun MA, Killam DA, Remick SC, Ruckdeschel JC. Lung cancer in patients seropositive for human immunodeficiency virus. *Radiology* 1990;175:341–343.
69. Tenholder MF, Jackson HD. Bronchogenic carcinoma in patients seropositive for human immunodeficiency virus. *Chest* 1993;104:1049–1053.
70. Escaut L, Liotier JY, Albengres E, Cheminot N, Vittecoq D. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. *AIDS* 1999;13:1419–1420.
71. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002;34: 1137–1142.
72. Keiser P, Nassar N, Skiest D, Andrews C, Yazdani B, White A, Hetherington S. Comparison of symptoms of influenza A with abacavir-associated hypersensitivity reaction. *Int J STD AIDS* 2003;14: 478–481.
73. Walensky RP, Goldberg JH, Daily JP. Anaphylaxis after rechallenge with abacavir. *AIDS* 1999;13:999–1000.
74. Gerard Y, Maulin L, Yazdanpanah Y, De La Tribonniere X, Amiel C, Maurage CA, Robin S, Sablonniere B, Dhennain C, Mouton Y. Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. *AIDS* 2000;14:2723–2730.